

REMARKS

Claims

By the present amendment, fifteen (15) claim have been amended, zero (0) independent claims have been added, zero (0) dependent claims have been added and zero (0) claims have been cancelled. Claims 1-17 are presently pending.

Support for the amendment to Claim 1 can be found at least at Claim 1 as originally filed and paragraphs 5 and 21 in the specification.

Support for the amendment to Claim 2 can be found at least at Claim 2 as originally filed and paragraphs 10 and 22 in the specification.

Support for the amendment to Claim 3 can be found at least at Claim 3 as originally filed and paragraphs 10 and 22 in the specification.

Support for the amendment to Claim 4 can be found at least at Claim 4 as originally filed and paragraphs 10 and 22 in the specification.

Support for the amendment to Claim 5 can be found at least at Claim 5 as originally filed and paragraphs 10 and 22 in the specification.

Support for the amendment to Claim 6 can be found at least at Claim 6 as originally filed and paragraphs 10 and 22 in the specification.

Support for the amendment to Claim 7 can be found at least at Claim 7 as originally filed and paragraphs 10 and 22 in the specification.

Support for the amendment to Claim 8 can be found at least at Claim 8 as originally filed and paragraphs 11 and 24 in the specification.

Support for the amendment to Claim 9 can be found at least at Claim 9 as originally filed and paragraphs 11 and 24 in the specification.

Support for the amendment to Claim 10 can be found at least at Claim 10 as originally filed and paragraphs 11 and 24 in the specification.

Support for the amendment to Claim 11 can be found at least at Claim 11 as originally filed and paragraphs 11 and 24 in the specification.

Support for the amendment to Claim 12 can be found at least at Claim 12 as originally filed and paragraphs 11 and 24 in the specification.

Support for the amendment to Claim 13 can be found at least at Claim 13 as originally filed and paragraphs 11 and 24 in the specification.

Support for the amendment to Claim 14 can be found at least at Claim 14 as originally filed and paragraphs 6, 18 and 19 in the specification.

Support for the amendment to Claim 17 can be found at least at Claim 17 as originally filed and paragraph 12 in the specification.

RESPONSE TO OCTOBER 11, 2006 OFFICE ACTION

In the Office Action dated October 11, 2006, Claims 1-13 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Office Action also rejected claims 1 and 14-17 under 35 U.S.C. § 103(a) as being unpatentable over Castelhano et al. (US 6,878,716) (“Castelhano”), optionally in view of Engel et al. (Inter. J. Pharm., 2000) (“Engel”). These rejections are respectfully traversed.

I. Rejection of Claims 1-13 under 35 U.S.C. § 112, second paragraph

Claims 1-13 were rejected in the Office Action under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Office Action states that Claims 1-13 are indefinite due to the language used in the claims. Claims 1-13 have been amended as suggested in the Office Action to more clearly reflect their status as compound claims. In view of the present amendments to Claims 1-13, applicants respectfully submit that the rejection based 35 U.S.C. § 112, second paragraph has been overcome and respectfully request withdrawal of the rejection.

II. Rejection of Claims 1 and 14-17 under 35 U.S.C. § 103(a)

Claims 1 and 14-17 were rejected in the Office Action under 35 U.S.C. § 103(a) as being unpatentable over Castelhano, optionally in view of Engel. The Office Action states that Castelhano teaches both 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine at column 66, lines 32-33 and the mesylate form as a pharmaceutically acceptable salt at column 21, lines 1-2 and 13. The Office Action concludes that although the claimed compound is not specifically named, it would have been obvious to select various substituents from the reference and combine them to arrive at the compound of Claim 1. The rejection of Claims 1 and 14-17 is respectfully traversed.

A. Requirements for a *prima facie* case of obviousness

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some teaching, suggestion or motivation, either in the nature of the problem to be solved, the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the references’ teachings.

Second, there must be a reasonable expectation of success. Third, the references when combined must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the cited references and not based upon the Applicants' disclosure. *See MPEP § 2143.*

The burden of establishing a *prima facie* case of obviousness lies with the USPTO. In determining obviousness, one must focus on the invention as a whole. *Symbol Technologies Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1576, 19 U.S.P.Q. 2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is: “[w]hether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success. ... Both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure.” *In re Dow Chemical*, 837 F.2d 469, 5 U.S.P.Q. 2d 1531 (Fed. Cir. 1988). Furthermore, references that teach away from the claimed invention are a strong indication of nonobviousness. *In re Soni*, 54 F.3d 746 (Fed. Cir. 1995).

As will be discussed in detail below, one of ordinary skill in the art, at the time of Applicants' invention, would not have been motivated to select the mesylate salt listed among twenty-five other pharmaceutically acceptable salts in Castelhano and combine it with the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine disclosed among at least 191 other distinct compounds listed in the Examples in Castelhano. Indeed, both the Castelhano and Engel references teach away from the very combination suggested by the Office Action.

Moreover, a person of ordinary skill in the art would not have had a reasonable expectation of success if they were to select 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine and the mesylate salt. Consequently, the Castelhano and Engel references, either alone or in any combination, do not establish a *prima facie* case of obviousness. Withdrawal of the presently pending rejection and allowance of all pending claims is respectfully requested.

B. No teaching, suggestion, or motivation to select and combine 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine and the mesylate salt in Castelhano

To establish a *prima facie* case of obviousness when combining multiple references or separate teachings within a reference, the Federal Circuit has clearly stated that “[t]he factual inquiry whether to combine references must be thorough and searching. It must be based on objective evidence of record. This precedent has been reinforced in myriad decisions, and cannot be dispensed with.” *In re Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430, 1433-34

(Fed. Cir. 2002); *see also*, e.g., *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) (“a showing of a suggestion, teaching, or motivation to combine the prior art references is an ‘essential component of an obviousness holding’ ”). *In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313 (Fed. Cir. 2000) (“Even when obviousness is based upon a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference.”). Indeed, the Federal Circuit has stated that the teaching to combine references must be “clear and particular.” *Winner Int’l Royalty Corp. v. Wang*, 202 F.3d 1340, 1348-49 (Fed. Cir. 2000). The absence of such teachings to combine references is dispositive of an obviousness inquiry. *Id.* Indeed, the MPEP specifically states that “[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination.” MPEP § 2143.01 (emphasis in original).

Applying these settled rules, the October 11, 2006 Office Action has failed to undertake the required “thorough and searching” factual inquiry to identify the “clear and particular” teaching within Castelhano which would motivate a person of ordinary skill in the art to modify the teachings of that reference as suggested in the Office Action. The identification of the specific teaching or motivation to modify a reference is a necessary component to establish a *prima facie* case of obviousness. In the absence of “clear and particular” teachings to modify a reference, obviousness has not been shown. *In re Chu*, 66 F.3d 292, 299, 36 U.S.P.Q.2d 1089 (Fed. Cir. 1995).

The Castelhano reference provides a list no less than twenty-six (26) different pharmaceutically acceptable salts and potentially many more based use of the phrase “and the like.” Castelhano at 20:64 to 21:16. One of the numerous listed salts is the mesylate salt. Castelhano at 21:13. The Castelhano reference also provides a very lengthy list of compounds among which is listed 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine.

Even though the Castelhano reference separately discloses both 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine and mesylate, a *prima facie* case of obviousness does not exist based upon Castelhano, optionally in view of Engel. First, Castelhano fails to provide any guidance or teaching regarding how a person of ordinary skill in the art would select the appropriate combination of the salt form and the particular compound. Indeed, with the disclosure of 26 different possible salts and approximately 191 compounds disclosed just in Examples 1-20 (spanning columns 65-81) and Tables 6-15 (spanning columns 93-118), this would encompass 4,966 salt/compound combinations – and

this only includes the compounds specifically identified in the Examples and Tables. Additionally, the “Detailed Description” of Castelhano in columns 10-19 describes hundreds of thousands of different additional compounds all of which could form a salt/compound combinations with the list of pharmaceutically acceptable salts provided in column 21.

Thus, despite the hundreds of thousands or perhaps even millions of salt/compound combinations, Castelhano has failed to provide any teaching or guidance regarding how one would go about selecting a single individual salt form from the list of 26 to be paired with one of the hundreds of thousands of compounds described in the “Detailed Description” to arrive at the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine hydrogen mesylate of Claim 1. Of the hundreds of compounds specifically named and identified in Castelhano, not a single one is paired with the mesylate salt form. Because Castelhano fails to teach how a person of ordinary skill in the art would select salt/compound pairs from hundreds of thousands of possibilities, reliance upon this reference is improper as the Federal Circuit has clearly stated that “[t]he prior art must provide one of ordinary skill in the art the motivation to make the proposed molecular modifications needed to arrive at the claimed compound.” *In re Lalu*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). No such motivation is present in the Castelhano reference.

This deficiency is not remedied by Engel. Relying upon Engel, the Office Action state that “one would be motivated to specifically use the mesylate salt because mesylate salts are known to be more soluble than many other known salts.” Office Action at p. 4. However, such a broad conclusion simply does not follow from the Engel reference. The most that can be drawn from Engel is that the mesylate form of one specific compound (LY333531) is more soluble than the hydrochloride form. It is simply not possible to select the mesylate salt form from the list in Castelhano, containing 24 other salt forms in addition to the hydrochloride form, based upon Engel. Contrary to the statement in the Office Action, one of ordinary skill in the art certainly can not conclude from the mesylate/hydrochloride comparison in Engel that the mesylate form is “more soluble than many other known salts” as the solubility of only a single salt was compared against the solubility of the mesylate form.

Even if Engel suggests to a person of ordinary skill in the art to select the mesylate form, which is not admitted, neither Engel nor Castelhano provide any teaching regarding how one would go about selecting a compound to be paired with the mesylate salt. Engel is directed to a single compound unrelated to the present application and Castelhano specifically identifies 191 compounds just in the Examples alone and hundreds of thousands of

compounds in the Detailed Description without any guidance regarding how to pair the listed salts with the disclosed compounds.

In selecting the mesylate salt form and 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine for a vast list of salt/compound options, the Office Actions has engaged in a classic exercise of hindsight – using the very teachings of the invention to pick and choose from a reference to reconstruct the claimed invention. This is prohibited. Thus, the absence of a any teaching in Castelhano to make the salt/compound combination suggested in the Office Action is fatal to establishing a *prima facie* case of obviousness.

C. Castelhano and Engel teach away from the combination of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine with the mesylate form

References that teach away from the claimed invention go against any finding of motivation to combine or modify the references. A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be led in a direction divergent from the path that the applicants took. *See, In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130, 1131 (Fed. Cir. 1994). There is no suggestion to combine, however, if a reference teaches away from its combination with another source. *Tec Air, Inc. v. Denso Man 'f Michigan, Inc.*, 192 F.3d 1353, 52 U.S.P.Q.2d 1294 (Fed. Cir. 1999). As will be discussed below, at the time of Applicants' invention, both Castelhano and Engel would have led a person of ordinary skill in the art in a direction divergent from that taken by the Applicants.

When viewed in their entirety, both Castelhano and Engel teach away from the subject matter of presently pending Claim 1. As explained above, Castelhano sets forth hundreds of thousands or perhaps even millions of possible salt/compound combinations. Of the compounds which are specifically identified in Castelhano, the vast majority are not in the salt form. Of the compounds which are in the salt form, the only identified salt is the trifluoroacetic acid salt. Castelhano at 14:3; 74:10-11; and 74:20-21. Castelhano teaches away by virtue of the fact that when the salt form of a compound is identified, it is not the mesylate form but the trifluoroacetic acid salt as this is the only saly/compound combination disclosed in Castelhano. Indeed, the preferred salt form in Castelhano, the trifluoroacetic acid salt, is not even listed with the other "pharmaceutically acceptable salts" of Castelhano. Not only does Castelhano fail to provide any salt/compound embodiments using the mesylate salt (or any other listed salts), but it teaches away from using any of the listed salt forms as

the only examples of salt forms in Castelhano are not provided in the list of “pharmaceutically acceptable salts.”

The disclosure in Castelhano fits squarely within the holding of *In re Baird*, 16 F.3d 380, 29 U.S.P.Q. 1550 (Fed. Cir. 1994) in which the Federal Circuit found that a reference taught away from the selection of a particular compound, which was disclosed among millions of compounds, when the reference focused on other preferred compounds. In *Baird* the Federal Circuit stated that “[a] disclosure of millions of compounds does not render obvious a claim to three compounds, particularly when that disclosure indicates a preference leading away from the claimed compounds.” *Id.* at 383. This statement is applicable to the present situation as the Castelhano reference discloses perhaps millions of salt/compound combinations yet indicates a preference for the trifluoroacetic acid salt form – a preference that leads away from the mesylate compounds of Claim 1. Moreover, the Federal Circuit in *Baird* recognized that a *prima facie* case of obviousness could not be made by a reference disclosing millions of possible compounds yet silent on how a person of ordinary skill in the art should select the variables leading to the claimed compound. *Id.* at 382.

Additionally, Engel also teaches away from the compound of presently pending Claim 1 as it cites two separate surveys which conclude that 43% and 44%, respectively, of the FDA commercially marketed salts were hydrochlorides. Engel at 240. Thus, based upon the survey data cited by Engel, a person of ordinary skill in the art would be led in the direction of using a hydrochloride salt since nearly half of all FDA approvals are for the hydrochloride salt form. A person of ordinary skill in the art would reach this conclusion even though the specific compound in Engel (LY333531) was preferably in the mesylate form as salt formation with new compounds is understood to be an “unpredictable exercise.” *Sanofi-Synthelabo v. Apotex, Inc.*, --- F.3d ----, slip op. at *5 (Fed. Cir. Dec. 8, 2006), 2006 WL 3613616.

D. No expectation of success if 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine was combined with the mesylate salt

In addition to the requisite teaching, suggestion or motivation to combine references, a *prima facie* case for obviousness also requires that a person of ordinary skill in the art have a reasonable expectation of success regarding the suggested combination of references.

Noelle v. Lederman, 355 F.3d 1343, 1351-52 (Fed. Cir. 2004), 69 U.S.P.Q.2d 1508; MPEP § 2143.02. The reasonable expectation of success must be found in the cited references and not in Applicants’ disclosure. *Id.*

Paragraph 4 of Applicants' specification states that “[i]t is an object of the present invention to provide a salt of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine that is crystalline, homogeneous, and stable product that has superior solubility properties.” Neither Castelhano nor Engel provide any teaching, suggestion or guidance on how to select a particular salt/compound combination that would achieve these goals. Although Castelhano gives a list of “pharmaceutically acceptable salts” that may be able to form a salt with the compounds listed therein, it will be unpredictable as to when a homogeneous, stable, crystalline product with superior solubility will be formed. This unpredictability is illustrated by the fact that the hydrochloric acid salt of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine is impure, unstable during storage (discoloration) and yields a precipitate of the base when dissolved in water. Moreover, the unpredictability associated with salt/compound combinations was recognized by the Federal Circuit as an indication of non-obviousness. *Sanofi-Synthelabo*, slip op. at *7. Indeed, the Federal Circuit specifically recognized that “salt formation was an unpredictable exercise that would require a chemist ‘to engage in experimentation to determine which salt would in fact be suitable.’” *Id.*

Thus, in view of the fact that the hydrochloric form of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine does not provide a homogeneous, crystalline and stable product with superior solubility, and the recognition by the Federal Circuit that the unpredictability of salt/compound formation is an indication of non-obviousness, a person of ordinary skill in the art would not have a reasonable expectation of success that the pharmaceutically acceptable salts of Castelhano could be combined with the other compounds described therein without additional guidance or teaching from either Castelhano or Engel. This additional guidance or teaching is not present in either reference.

E. Unexpected results from the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine mesylate salt

“One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of ‘unexpected results,’ *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward – that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as

chemistry, where minor changes in a product or process may yield substantially different results.” *In re Soni*, 54 F.3d 746, 750, 34 U.S.P.Q.2d 1684 (Fed. Cir. 1995).

The 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine hydrogen mesylate of Claim 1 exhibits unexpected results. As shown in paragraph 30 of the specification, the base form of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine had a solubility of 0.0059 mg/L in purified water while the α and β polymorphs had respective solubilities of 77 mg/L and 18.5 mg/L. Thus, the mesylate form of the α and β polymorphs had an increase in solubility of approximately 13,000 and 3,100 times, respectively, relative to the base form. This enormous increase in solubility of the mesylate form over the base is entirely unexpected. Although solubility is generally increased when an anionic compound is in a salt form, a person of ordinary skill in the art would not anticipate that the water solubility would increase by such a substantial amount.

Additionally, it is also entirely unexpected that the mesylate salt of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine would exist in two separate polymorphic forms having the properties (XRPD, IR spectrum and melting point) described in the application at paragraphs 10 and 11.

Finally, it is unexpected that the mesylate salts of the two polymorphs of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine would exhibit the desired crystallinity, stability and purity in view of the fact that salt formation is an unpredictable exercise requiring extensive experimentation. These aspects of salt formation for pharmaceutical products was recognized not only by the Federal Circuit in *Sanofi-Synthelabo* but also in the Engel reference. Due to the unpredictable nature of salt formation, Engel was required to undertake substantial testing on seven different salt forms.

III. Conclusion

In view of the amendments to Claims 1-13 as suggested in the Office Action, Applicants respectfully submit that the rejection of these claims based upon 35 U.S.C. § 112 has been overcome and withdrawal of the rejection is respectfully requested.

Because every element required for a *prima facie* case of obviousness as set out in the MPEP § 2143 has not been met (*i.e.*, no suggestion or motivation to modify or combine the cited references and no likelihood of success), the Office Action has not established a *prima facie* case of obviousness. Withdrawal of the rejection of Claims 1 and 14-17 under 35 U.S.C. § 103(a) as unpatentable over Castelhano, optionally in view of Engel is therefore

respectfully requested. Upon withdrawal of the currently pending rejections, Applicants respectfully request allowance of all pending claims.

VI. Concluding Remarks

It is to be understood that no admission is made nor implied by the present amendment as to the fact that the cited references may be relevant. Indeed, this amendment is made *solely* to expedite the prosecution of the present application.

Applicants submit that in light of the amendments and arguments provided herein, all pending claims of the present Application are in condition for allowance. Applicants respectfully request entry of the proposed amendment and allowance of the claims. If, in the opinion of the Examiner, a telephone conference would help expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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